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The Expanding Role of IMMUNOLOGY

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FOREWORD

If survival of the fittest seems to explain the present status of living things in a competitive world, it may be argued that immunological forces more than brute strength dominated the contest in higher forms of animal life.

No class of livestock is free of the forces of immunity. A simple unit of life such as the virus particle generates antibodies in the largest and most complex of host animals and pits its offense against the vigor of the host's defense. A larger parasite may likewise join similar contests with both its predators and its host animals.

Man and animals not only owe their survival to the immune phenomenon, but also use it to their own disadvantage in combatting irritants which, as a rule, pose little danger to them but cause allergic reactions.

We have known something about immunity for 160 years but understand little about it. Because of its diverse forms of expression, there is little wonder that immunity seems complex. Accumulating evidence shows that the immune phenomenon has a wide range of applications, some of which do not involve disease.

It is the purpose of this report to examine the elemental facts of immunity in broad perspective.

The role of immunity in combatting disease by no means tells the whole story of the science, but is a good approach to the subject.

The information in this report was furnished by the Animal Husbandry Research Division, Animal Disease and Parasite Research Division, Animal Inspection and Quarantine Division, and Crops Research Division of the Agricultural Research Service.

THE EXPANDING ROLE OF IMMUNOLOGY

Immunization of livestock dates from Pasteur's development of effective vaccines against anthrax, rabies, and one strain of fowl cholera three quarters of a century ago. The immunization method has been used with varying success for the control of many diseases and now is considered as basic to some branches of animal husbandry as good feeding and management.

Immunization is invaluable in protecting animals against hog cholera and rabies, for example. Brucellosis, anthrax, blackleg, malignant edema, equine encephalomyelitis, bluetongue, laryngotracheitis of poultry, virus diarrhea, leptospirosis, Newcastle disease, Rift Valley fever, rinderpest, swine erysipelas, and some other diseases are controlled, at least to some extent, by immunization.

Research is constantly adding to the list of diseases that can thus be controlled.

Through immunological principles, researchers are constantly uncovering new diseases, viruses and bacteria that had not been recognized as such. Bovine leptospirosis and canine infectious hepatitis were not fully appreciated as diseases until a few years ago, but when specific serological tests were developed, both diseases were found to be widespread and economically important. Recently a new strain of fowl cholera, not responsive to Pasteur's vaccine, was identified and controlled experimentally with a killed vaccine.

Vaccination is an important tool in protecting individual animals from such contagious diseases as hog cholera, which occur year after year in the same areas. It is a more dramatic curb of epizootics, protecting both the uninfected herds and flocks in epizootic areas and susceptible livestock in disease-free threatened areas. During an epizootic of Newcastle disease of poultry a few years ago, Federal and State programs brought the disease under control through a combination of quarantines, flock vaccination in each new area of infection, and disposal of infected birds.

Immunology also has an important role in eradication programs designed to eliminate all traces of a livestock disease from an area. Serological tests spot the problem areas and determine which herds and animals must be dealt with. A composite milk test for a dairy herd will show, for example, whether any cow has brucellosis. Thus sampling and testing at a few creameries and milk stations shows which herds within the milkshed must be quarantined, individually tested, and cleaned up. Also, area-wide spot testing for brucellosis and tuberculosis locates herds harboring the diseases. So immunology is helping in various ways to free the nation of costly diseases.

The development of immunity is a normal body response not always dependent on infections. It is intimately related to other basic functions. Learning about the one sheds light on the others.

We have long practiced immunization on every class of livestock, yet have only recently begun to understand many of the principles of immunity. Even today we must rely on theory for much of the explanation. But we are probing the unknown for better basic understandings and are rewarded time after time with important immunological breakthroughs. Breakthroughs in antiinfection technology. Breakthroughs in blood chemistry. Breakthroughs in immunogenetics. And breakthroughs in immunophysiology, including hypersensitivity, tumor immunity, tissue and organ grafting, and radiation biology. And as we probe into the cell, studying immunological processes of the most elemental organized units of living matter, we knock on the door of the deepest mystery of all, how life begins.

KINDS OF IMMUNITY

Immunity as described by early investigators included such defenses as exclusion of the pathogen by the animal's impervious covering (skin) and denial of substances the would-be parasite must obtain for its metabolism or for acquiring nutrients from its host.

An animal also defends itself actively from infection through the direct attack on and consumption of invading disease agents by the body cells. In the blood stream, the invader is destroyed by the white corpuscles. In the body tissues, it is attacked by the fixed or slightly mobile cells of the lymph glands, lymph nodes, spleen, liver, bone marrow, and some other tissues and organs.

Immunity, however, has come to mean degrees of resistance to a disease. Major interest centers on ways of artificially increasing inadequate resistance. The procedures and mechanisms for accomplishing this are called immunization.

The defending animal achieves active immunity by building a supply of antibodies to antigenic pathogens. Most pathogens have antigens--component chemical substances which cause specific antibodies to form against those antigens and tie up or destroy them. The antigen-antibody mechanism is described in the next section.

The individual may also receive passive immunity through the injection of antibody-bearing blood serum from an animal which is immune to the disease. This gives immediate but short-lived protection.

Toxins given off as byproducts from the growth of parasites, and the venoms of snakes and insects that cause great harm to an animal may generate antibodies and be neutralized by them. These antibodies are the antitoxins and antivenins injected into the body to counteract the toxins and venoms.

The immune relation between an infective agent and its host grows in complexity with the complexity of the organism. The protein jacket of a virus particle contains a number of antigens. The more complex Rickettsia, bacteria, and protozoa contain more antigens. The larger internal parasites infesting animals--the many-celled nematodes, other parasitic worms, and the larvae of some insects--have many antigenic molecules, each attacked by the host's antibodies.

Not all immune responses are helpful. For example, antibodies generated against transfused blood and against transplanted tissues from other animals (normal substances in an abnormal situation) and antibodies formed against natural substances such as plant juices and danders (allergens) can cause great harm. These reactions are quite important not only to animal health but also to understanding basic cell chemistry.

Many revolutionary new developments in immunology are based on antibody production.

THE ANTIBODY PHENOMENON

Recovery from a bacterial or viral infection often occurs because the animal has immunized itself by building a supply of antibodies which tie up the substance, known as antigen, contained in the pathogen. This conditions pathogens for easier disposal by the total defense mechanism.

Antibody buildup is a normal body reaction to infection. The antigen, which is a molecule of protein or related compound, induces the body of a host to form a specific molecule of globulin protein (the antibody) for which the antigen has an affinity. The antibody combines with its antigen, conditioning the pathogen in some way so it can be acted upon by complement. Complement is a normal fraction of the blood serum comprised mostly of proteins. This keeps the pathogen from pursuing its normal infective course. The host thus becomes immune to the disease. Immunity to some diseases is short lived, but immunity following recovery from hog cholera and a number of other diseases may last a lifetime.

The antibodies are developed largely in the spleen, liver, lymph nodes, bone marrow, and other lymphoid tissues under stimulus of the antigen. The antibodies are carried in the blood serum and other body fluids. Both antibody and complement molecules are small in comparison with body cells.

Some degree of protection can be established by the introduction of artificial preparations of dead, weakened, or even virulent organisms. This is called vaccination. Supplemental vaccinations are sometimes used to boost antibody production.

Some viruses appear to be so closely related to certain others that exposure to the one will give protection against the other. The cattle disease VD (virus diarrhea), to which hogs are immune, and the swine disease hog cholera, to which cattle are immune, have that relationship. The one antigen seems to precondition the antibody-forming cells to the related antigen.

Pigs experimentally inocculated with live VD virus developed a cross protection against hog cholera. In a similar way, cattle inoculated with hog cholera virus had a cross protection from VD.

A similar cross protection occurs in poultry. Antibodies to fowl cholera or to fowl typhoid protect the poultry from pullorum disease.

The phenomenon of antibody production has special interest because in recent years it has opened up or contributed to a number of important fields of study. Some of these fields are: immunocytology, including allergy; immunofertility or immunology of reproduction; immunogentics; immunochemistry, including DNA and RNA metabolism and protein synthesis; cell and tissue culture; tissue and organ grafting; and radiation biology.

VACCINATION

Vaccines were developed long before anyone understood how they operated. Through the years, many new vaccines have been developed, many of those made safer and more effective, and vaccination procedures improved. Today's innovations are steadily advancing the livestock industries. Three examples will make the point.

One of our earliest livestock vaccines (the one for fowl cholera) was only partially effective until recently, when research disclosed a previously unknown strain of the bacterium and provided a more complete vaccine. As another case in point, the live virus for equine encephalomyelitis (sleeping sickness) is too dangerous to use in vaccines, but research developed a killed-virus vaccine which is safe and effective. And a vaccine for Johne's disease, which gives good immunity in cattle, has repeatedly caused a false positive reaction to the tuberculin test in cattle. That interfered with the tuberculosis-eradication program. Recent study has shown, however, that vaccination early in calfhood will adequately immunize the animals against Johne's disease without interfering with tuberculin tests at about 20 months of age.

In this connection, it should be mentioned that antigen-antibody reactions have been used experimentally for a number of purposes other than disease protection. For example, protein can be injected to produce antibodies which in turn can be used in the analysis of complex mixtures of proteins. It is possible that other important nonpathological applications of immunization will be evolved in the future.

Two recent advances in vaccines are particularly noteworthy and will be described here. One is the development of safer yet effective modified live-pathogen vaccines. The other is the successful propagation of animal tissues and cells in glass flasks--that is, under controlled laboratory conditions--as host material for growing pathogens for vaccines.

Modified-Pathogen Vaccines

For many years the swine industry was sustained by a program of immunization against hog cholera with a virulent live-virus vaccine. There were dangers in this practice, however, for the virulent organisms frequently killed the animals rather than saving them. Moreover, the vaccine perpetuated the virulent hog cholera virus. A few years ago, scientists were successful in developing a modified form of the virus which was effective and much safer to use.

Viruses lose a little of their virulence when propagated in certain animal species which are naturally resistant to the disease. A rabbit inoculated with the hog-cholera virus modifies it. The modified virus recovered from the rabbit and reinoculated consecutively into other rabbits becomes progressively less virulent. Eventually the virus becomes sufficiently modified to use safely, yet is still effective for vaccination. Modified live hog-cholera virus prepared in this way has come into wide use within the past 8 or 10 years, marking one of the most significant recent advances in the control of livestock diseases. This type of vaccine is also being used against other diseases--rabies, canine distemper, distemper of mink, and Newcastle disease of poultry.

Producing Vaccines in Glass

The new techniques of culturing animal cells in glass commonly referred to as tissue culture are beginning to revolutionize the method of producing vaccines.

Thousands of animals have been required by the biologics industry to propagate pathogenic viruses and bacteria for vaccines and also to provide the immune serum needed for immunization and testing. Due to the animals' differing responses to infection, their vaccines vary greatly in potency. Also, animals with multiple infections sometimes contaminate vaccines, thus spreading disease.

Producing vaccines in live animals means keeping a great animal mass for the sake of a small amount of compatible host tissue to grow the micro-organisms on. On the whole, this is a cumbersome and costly practice. A 200-pound hog, for example, may be used in producing hog-cholera vaccine, although only a few pounds of the hog's tissues and blood actually are involved in the production.

Many attempts have been made to grow pathogens on artificial medium, but they often lost virulence under those conditions. Researchers have also tried for some time to grow the needed organs, tissues, or cells artificially and use them as hosts for cultures. Recently the ideal combination of nutrient formulae, temperatures, processing methods, and other factors was discovered for growing some greatly needed cultures. Now it is possible to keep cells or tissues alive and growing in glass containers.

Some viruses and Rickketsia develop as normally on these cultured tissues as in the live animal. Sterile conditions are provided and the pathogenic purity of the cultures is rigidly controlled. Now, without sacrificing a single animal, a fresh hog kidney from the slaughterhouse can yield under flask culture several hundred times as much hog-cholera vaccine as did a live animal under the old procedures. At the Plum Island Animal Disease Laboratory of the Agricultural Research Service, Greenport, L. I., N. Y., bovine kidney and tongue tissues have been successfully cultured and the virus of foot-and-mouth disease modified (as discussed in this section) so they will grow on the tissue culture.

A variety of livestock vaccines are thus being produced from a limited amount of original animal tissue.

SEROLOGICAL TESTING

The fact that a disease antigen will cause antibodies to be produced and will react with them is the basis for certain diagnostic testing. This is called serological testing because it usually involves the use of serum.

It is possible to use a known antigen to identify its antibody in an animal's blood serum or to use known antibodies to identify their specific antigens.

When the antigen and antibodies are homologous, the cells bearing the antigen become linked by molecules of antibody and show secondary characteristics such as precipitation or agglutination. These reactions are specific evidence of the disease, since antibodies would not be produced unless the animal had been exposed to the antigenic pathogen.

Fluorescent Testing Technique

While many tests give clearcut results, and perhaps most tests do so under some conditions, some test reactions occur obscurely and require skillful and time-consuming interpretation. A new technique now coming into wide use simplifies the interpretation of such tests by making reaction products fluoresce.

To use the method, a test serum containing a known antibody can be treated with fluorescent chemical which adheres to the antibody protein. When the tagged antibody encounters its antigen counterpart (a bacterium, virus, or inert protein which generated the antibody) in a serological test, the fluorescent antibodies concentrate around the antigen and fluoresce brightly in the presence of ultraviolet light. A positive reaction can be observed easily in tissues under a microscope, although that might be difficult to see without the fluorescent tag.

This method, with some variations, has been used with encouraging results for the past few years and may greatly extend the scope of serological diagnosis.

An Exceptional Serological Use

In view of the role of certain fungi, pollens, and toxic herbs as allergens, it is not surprising that scientists have used the principles of immunology in studying plants.

Researchers have shown that reagents for serological testing do not have to be of animal origin. For example, an agglutinin for the A factor in human blood has been found in two species of lima beans and an agglutinin for the B factor found in a species of mushroom. The search for specific anti-antigen factors appears, therefore, to be a wide-open field for research. Synthetic chemicals as well as plants offer possibilities.

In one study a few years ago, a group of researchers of the Agricultural Research Service and the Nebraska Agricultural Experiment Station used rabbits to produce antisera to a number of plant pathogens. The antisera were used in a plant breeding program to test plants for susceptibility to certain virus diseases.

Rabbits were given injections of prepared juice from plants infected with barley stripe mosaic, brome mosaic, potato X disease, tobacco mosaic, elm ring spot, and cucumber mosaic--one disease per rabbit. Rabbits are immune to these plant diseases but develop specific antibodies, just as they respond to the chemically similar animal-disease viruses.

Antibody-bearing serum is extracted from the rabbits as needed and tested with the juice of each plant after the plants have been inoculated with the disease in question. If a precipitate forms, the plant has the disease to which the donor rabbit was immunized. Such plants can be discarded and only resistant ones further used. This simplifies and expedites plant breeding for disease resistance.

Another research team is trying to develop techniques for separating and purifying the various species and strains of plant viruses and to improve their survival so antisera can be made which will precisely identify and classify the viruses. Unpurified plant juices now used might contain two or more viruses plus some normal plant proteins, and would, therefore, produce a mixture of antibodies in a rabbit. Moreover, it has been difficult, so far, to extract and use certain unstable viruses by present techniques because they change before antibodies can be produced.

Crop researchers of the Agricultural Research Service and the North Dakota Agricultural Experiment Station used serology as a new analytical technique in discovering the basic reason for a plant's susceptibility to rust disease.

Proteins were suspected as a factor, so the scientists immunized rabbits against the globulin proteins from various varieties of flax and globulin proteins from various races of flax-rust fungus. Rabbits generate antibodies to globulin proteins, so several antirust and antiflax sera were prepared. Tests with these sera showed that a rust fungus and the flax plants susceptible to it had a protein in common and that plants lacking the rust protein have a physiological or hypersensitive type of resistance to the fungus.

This simple use of serology gave information it would have been difficult and very costly to get by conventional protein analysis.

BLOOD'S ANTIGENIC PROPERTIES

Immunity was originally viewed as a blood phenomenon. And since immune reactions of the blood raised urgent problems, much of the early study of blood chemistry was aimed at learning more about the phenomenon. In studying both animals and men, immunologists explored not only the blood, but also tissue cells and a variety of natural and experimental substances having antigenic (antibody-producing) properties. These studies grew into an important field of specialization known as immunochemistry.

Three fractions of the blood are involved in immunization--the white cells (leukocytes), the red cells (erythrocytes), and the plasma (liquid portion). In this connection, chief attention will be given to the red cells, which contain many antigens, and the plasma, which is involved in the antigen-antibody reactions.

The early immunological studies on the blood were primarily concerned with blood types, for these posed many urgent problems. But in the course of research much attention has been given to the antigens of the white cells and to the plasma. Now, much has been learned about these, and their important role in immunization is becoming better appreciated.

Different species have different numbers of antigens of the red blood cells. In man, there are at least nine blood groups, each consisting of one to three antigens and possibly more. Cattle, on the other hand, have at least 11 blood groups comprised of some 80 to 100 antigens. Other classes of livestock have similarly complex blood systems.

Blood antigens are of practical importance in blood transfusions. Bloods must be crossmatched to avoid transfusing blood with certain antigens into a recipient whose blood contains antibodies against it. If an incompatible blood is transfused into an individual, the donor's red cells are destroyed.

Hemolytic disease resulting from Rh-factor differences between mother and offspring is another case of antibody-antigen conflict. In such cases, the mother produces antibodies against the young's Rh factor, and those antibodies destroy the offspring's red cells. Hemolytic disease occurs not only in humans but also in animals--the horse, for example. It is interesting, however, that in studies by the Agricultural Research Service, hemolytic disease could not be produced even experimentally in cattle.

In humans, the antibodies reach the child through the placenta before birth and to a limited extent through the mother's milk after birth. Horses, on the other hand, transmit their antibodies only in the milk after birth.

Researchers want to learn more about antifetal blood factors in all classes of livestock. This might point a way to improve survival rates in swine and some other species.

A careful watch will be made during such studies for other relationships between the blood antigens of mothers and their young which may have a bearing on the well-being of the offspring.

Much of the blood-antigen research is being done on testing techniques, cell matabolism, genetics, and other special subjects treated elsewhere in this report.

PROBING THE PRINCIPLES OF CELL CHEMISTRY

Some scientists think that the immune reaction which takes place in cells is close to the physical and chemical processes which initiate life. By studying this immune reaction, they hope to learn how viruses (alien molecules) stimulate the production of antibodies (proteins) in the host, and, on the other hand, convert cell contents into more virus (related but different from proteins). They also seek to learn how genes (vehicles of inheritance) duplicate themselves in reproduction, and in general, how cell chemistry regulates life.

Within the last few years, tissue cells have been found to contain natural antigens different from the blood antigens. During the decades of research on blood, many antigens were identified and studied, but little progress was made in understanding differences between individuals of one species and between organs and tissues of the same individual as to the numbers and kinds of natural antigens in the tissue cells.

Cell chemistry and physiology are now being investigated intensively. And cell immunology is being studied along with the other basic cell processes.

Why does one fertilized egg develop into a man, another into a cow, and a third into a sheep? Why does one specialized cell in the embryo develop into one organ and another into a different organ? And why do the various antibodies generated in an individual differ essentially?

It is puzzling that the end products can be so different on the whole and yet, in some particulars, so nearly identical--as chemically related, for example, as we have found the blood factor A in man, factor J in cattle, and factor R in sheep.

Genes, vehicles of inheritance, do not by themselves govern these things, for we have learned that cell cytoplasm may also play a role. Proteins are major constituents of the cell, but they alone do not make these determinations, for we now know that polysaccharides have some effect.

We have recently learned, however, that the configuration of the long chain of amino-acids comprising antigens seems to make an important difference between antigens. The difference between hemoglobin C and hemoglobin B in blood, for example, is due to a change in configuration brought about by the substitution of lysine for glutamic acid. This is an example of the sort of difference that may distinguish one antigen from another.

It is important to study an antibody's way of singling out an antigen and combining with it. Possibly the fluorescent-test technique or some other method of tagging might help identify and follow antibodies in living cells. Or tagging nonpathogenic proteins and introducing them into cells might make it possible to observe them in the process of generating their specific antibodies and uniting with them. Learning the ultimate disposition of such protein molecules through cell metabolism might answer some of the questions.

It is important to study viruses, antigens, and genes, as a group, for they have some chemical features in common, and discoveries about one might help explain the others. It is reasoned that discovering how a virus causes antibody formation might suggest procedures for study of virus replication and gene reproduction. Also, genes cause the production of blood-cell antigens (as explained in the section on Genetic Factors in Immunity) and in fact the genes determine other cell proteins as well.

If we learn how to control the duplication (division) of genes, we should then learn how to cause cells to reproduce at will--in other words, to make an animal or plant grow as we wish--and how to duplicate an individual and perpetuate a clone or species.

Having complete knowledge of the chemistry of these processes might even enable us to synthesize or alter genes, cells, and individual organisms to specifications. But more immediately, it may teach us what causes radiological damage to cells and how to prevent it, what causes aging and how to prolong useful life, and what causes malignancy and how to control it.

HYPERSENSITIVITY

Animals as well as man are subject to distressing hypersensitivity to certain proteins and other chemicals. This allergic condition develops locally in cells where the stimulus occurs and is properly a phase of cell chemistry discussed above.

The individual's response may be either a typical immune reaction or may resemble it. The typical antigen-antibody mechanism is involved in the former kind of cases, but not in the latter.

Unlike an infectious organism, the excitant in these cases is not immediately and directly harmful. The antigen does not cause a reaction at first, but preconditions the cells for a strong reaction on the next or later contacts. Susceptible individuals react excessively. The antigen is not toxic in itself, but the immune reaction sometimes yields toxic byproducts that are harmful, sometimes fatal. Various allergic symptoms are the price one pays for the overefficiency.

Typical immune-type hypersensitive reactions may be caused by certain foods, drugs or other chemicals, pollens, dusts, danders, poison ivy and other plant juices, antibiotics, and injections of immunizing serum from a different species. Antibodies are formed and react with the sensitizing substances. Toxic reaction products seem to cause the hypersensitivity, but spasm of the smooth muscles causes the distress. Itching, sneezing, excessive secretions, swelling of tissues, and other distressing symptoms develop. Sensitivity occurs immediately on the second or later contact of the irritant with the cells, increases with subsequent exposures, and may cause shock or even death. Cells are not destroyed, however, and the condition is generally short lived. Slow injection or successive small injections of the antigenic substance into the individual, especially into the bloodstream gives relief.

Hypersensitivity is an individual matter and any person can experience immune-type hypersensitivity to a variety of substances. The condition is best known in humans, but some scientists think immune hypersensitivity may play a part in some unexplained unthriftiness in livestock. This is further discussed under "Internal Parasites and Immunity."

On the other hand, there is a quasi-immune type of hypersensitivity that is symptomatically similar to the foregoing type and quite common in livestock. Cattle which have built antibodies to the tubercle bacillus react strongly to the proteins in the tuberculin serum when it is used in testing for tuberculosis. Also, recontact with the pathogenic agents or immune sera of undulant and typhoid fevers, tularemia, and glanders sets up hypersensitive conditions in the animals. These reactions differ from the immune type of reactions discussed earlier in that the sensitive cells are not known to produce antibodies to the irritant.

INTERNAL PARASITES AND IMMUNITY

Throughout most of the history of immunological science, students and practitioners have been chiefly concerned with micro-organisms which produce and respond to immune effects in higher animals and with blood antigens which also cause immune reactions. Then inanimate antigenic substances came under investigation. Only in recent years have our researchers turned their attention to immune effects involving larger parasites--the nematodes, certain other worms, and insect larvae that infest the organs and internal tracts of livestock.

Many had observed that dogs and other animals generally are infested when young but less so in adulthood. One researcher observed a pronounced shift in the serum proteins of animals under study as they became heavily parasitized--a change from alpha and beta globulins to gamma globulins. Antibodies are mostly gamma globulins.

Investigations in the U.S. Department of Agriculture and foreign laboratories demonstrated that cattle which survive lungworm infections often become immune. Recently a British research team has produced a practical commercial vaccine which can be given by mouth to susceptible cattle. The vaccine is prepared by exposing a larval stage of the cattle lungworm to X-rays. Irradiated larvae undergo only partial development in the host and produce a solid immunity without causing clinical disease. Subsequent studies in the U.S. Department of Agriculture and other laboratories have shown that vaccines may be produced for other nematode diseases by suitable irradiation of larval stages.

Antigens present in various organs and tissues and in the secretions and excretions of many-celled parasites are being studied for their ability to act as "vaccines." Antigens which are believed to be important in immunity to certain cattle nematodes have been found in molting fluid which is secreted to facilitate each change in the life cycle of the parasite. Antigens have been extracted from various organs and tissues of the swine kidney worm, principally the excretory glands, intestine, and esophagus. These substances precipitate on contact with antibodies present in the serum of swine infected with this nematode and are being studied as experimental "vaccines" in pigs.

The cultivation of helminth parasites in glass tubes is a recent development which may have important applications in the field of immunology. Certain nematodes grown by this technique have been shown to produce antigens which may be identical to those normally produced by the parasites within the host. In the near future large numbers of parasites for immunological studies may be easily harvested from cultures instead of experimental animals.

Adult gastro-intestinal nematode parasites may be expelled from the host by a hypersensitive reaction known as "self cure." Conditions for hypersensitivity are set up as those parasites develop to adulthood. The hypersensitive reaction is triggered when the animal picks up additional immune larvae and is characterized by a local inflammation response of the gut mucosa and a significant rise in blood histamine.

GENETIC FACTORS IN IMMUNITY

By finding that there are differences in blood between individuals, Landsteiner paved the way in 1900 for the later recognition of the ABO blood system in man. Others recognized that the antigenic differences are an index to individuality. And the discovery of Von Dungern and Hirszfeld in 1910 that these differences are inherited paved the way for the modern concept of immunogenetics.

Genetic studies have shown that the factors for blood antigens are handed down from generation to generation in a Mendelian fashion, meaning that the antigens are determined by genes. In the simplest pattern, a single antigen is determined by a single gene. And the pair of corresponding chromosomes ("bundles of genes") which the animal has determines which two genes (and, therefore, which two antigens) are held. For example, of the three possible genes, A, B, and O, for the best-known blood group in man, an individual can possess factors AA, AB, AO, BB, BO, or OO. The corresponding blood types are known as A, AB, A, B, B, and O.

The inheritance pattern is not so simple, however, for the 8 or more other blood groups comprised of more than a score of blood antigens in man. Nor is it simple for some of the 11 or more blood groups comprised of 80 to 100 antigens in cattle, and the similarly large number of groups and antigens in the other classes of livestock. Certain genes may control or at least influence two or more antigens. And certain antigens may be affected by two or more genes.

Although many antigens will occur in the red cells of a man, cow, hog, chicken, sheep, or other animal, probably only a fraction of the antigens have been detected by serological tests. It has taken many studies to discover the factors now known to occur in the animal species studied so far. Still other factors and their controlling genes may come to light.

Because of its genetic basis, blood typing is practically the equivalent of finger printing for identification. There are tremendous odds against any two cows, for example, other than identical twins having exactly the same blood type. Fraternal twins are often an exception. Because their bloods mix while they are in the uterus, fraternal twins may share all of the antigens of both individuals.

The many antigens--more than a score in humans and 80 or more in cattle--can be brought together in millions of combinations. Each combination is a blood type. Literally hundreds of genes exist, each causing different blood factors, but only a small fraction of those genes can be present in one animal.

The fact that each blood antigen arises from one or more genes means that an individual inherits half of his blood factors from one parent and half from the other. Each of the individual's blood factors must, therefore, be found in one parent or the other. This has led to blood testing to determine whether an infant can be the offspring of two specified parents (as in the case of confused identity of babies in hospitals) or more frequently testing to solve paternity disputes.

The widespread development of artificial insemination in cattle and some other livestock often raises questions of parentage. Laboratories for the study of animal blood groups are able to type the blood of dairy animals in question and resolve such controversies.

Another important genetic problem has been studied. The conflict between a mother and her fetus in hemolytic disease of the newborn suggested that infertility of a female might be due to her immune reaction to certain semen antigens. Sperm can generate antibodies when injected into the tissues or circulation of an animal. In a joint study by the Agricultural Research Service and the Wisconsin Agricultural Experiment Station, bull semen was injected into a cow's bloodstream and antibodies produced there. Semen of the same bull was then treated by adding the antibodies and used to inseminate six cows. Five either failed to conceive or didn't retain the embryo. The sixth conceived but her embryo deteriorated. Two controls inseminated with semen treated with serum not containing antibodies conceived normally.

This study showed that semen antigens are attacked when in contact with their specific antibodies. But another phase of the study showed that these same antibodies, when present in the cow's bloodstream, did not interfere with conception. It will take further study, however, to learn whether some cows have antibodies which act against certain sperms in utero.

Known relationships between two or more characters in an animal or plant often are valuable tools in the hands of geneticists, especially when one of the characters can be easily identified and measured. The measurement of the one trait then indirectly measures the other. With this in mind, livestock geneticists have been trying to discover economic traits correlated with blood type, since blood type is easily determined at an early age.

One such study in poultry genetics is being made by the Texas Agricultural Experiment Station and the Agricultural Research Service. It has shown that in chickens, a certain combination of genes for the B system of blood antigens appears to give a slight measurable advantage in some characteristics--for example, hatchability of fertile eggs, weight of bird at a given age, and survival rate. The Texas experimental poultry flocks are being built up to check these preliminary findings in sibs that are more uniform genetically.

Cooperative studies of dairy cattle by the Agricultural Research Service and some of the State agricultural experiment stations are now under way to determine possible genetic relationships between blood types and various economically important characters such as length of life, milk production, weight-gaining ability, and the like. Some reports have been published of slight associations of blood groups and production in cattle.

Relationships of this kind are also being sought in sheep and swine.

Despite the small success so far, the search will be continued. Only limited relationships are anticipated, however, since there are many genes exerting effects on production, but few blood-type genes to correlate with them.

SOME OTHER AVENUES OF RESEARCH

Three serious health threats to man and animals, and the mounting public concern about them, have touched off some immunization research of great current interest. The problems are cancer and other tumors, radiation damage, and defacements calling for repair grafting.

The first is an old but increasing problem of humans, and of livestock as well. The latter two are dangers inherent in modern warfare and the rapid pace of present day living--that is, from atomic radiations, from the therapeutic use of X-rays, radium, and other radiations, and from various defacing injuries.

Tumor Immunity

Immunologists have dreamed of producing an antiserum to malignant tissues which would react with and destroy the wild cells. Years of effort to understand tumors yielded little but frustration until some recent research kindled new hope.

There is considerable evidence that some malignancies are caused by viruses. Researchers at the Regional Poultry Research Laboratory of the Agricultural Research Service at East Lansing, Mich., found, for instance, that they could transmit visceral lymphomatosis (a form of poultry cancer) to uninfected chickens by injections of blood serum and tumor extracts from lymphomatous birds. The scientists found that the disease could be transmitted even from some birds which had no evident disease symptoms, indicating that those birds were infected with the virus without showing overt symptoms. Some of the birds later developed symptoms, indicating that not all of them were immune.

This immunity may be caused by two phenomena. The first is genetically controlled or natural immunity. The second is a resistance or immunity due to the development of antibodies provoked by the specific virus. These phenomena involve different mechanisms. Each of them separately has an important effect, but operating jointly may achieve more than the sum of those effects.

The fact of genetic resistance was learned when the scientists succeeded in producing resistant and susceptible lines of chickens by inbreeding.

Then came a breakthrough of the cancer barrier. Susceptible hens, vaccinated with a dilute preparation from diseased chicken livers, produced chicks which initially showed high resistance to lymphomatosis when tested with potent injections of the virus. The resistance, however, was only temporary. The hens had apparently built up antibodies to the virus and passed those antibodies through the eggs to their chicks. This does not mean that the problem of poultry lymphomatosis has been solved, but does mean that the immune reaction is a factor in this specific form of malignancy. And that knowledge provides one more tool with which to attack the unsolved problem.

A pair of recessive genes--that is, identical genes on two chromosomes--was found to cause resistance to Rous sarcoma, another tumor virus. Birds lacking this pair of genes or having just one of them are susceptible. The study also showed that a single dominant gene gives complete resistance to a blood cancer, erythroblastosis.

This is an adaptation of the familiar live-virus immunization long used against other diseases, including hog cholera, rabies, smallpox, and tetanus. The immunity, however, operated against only a certain type of cancer--cancer that could be combatted by tying up a causative pathogen.

Not all malignancies are caused by viruses. It is believed that a tumor sometimes originates through mutation of a cell--that is, by an imperfectly reproducing gene changing one of the cell enzymes into a new product.

Such a product, having originated in the individual, would be indigenous to him. The body does not commonly generate antibodies to its own native constituents. This might explain why the mutated gene and the cell it belongs to can continue to reproduce without interference from antibodies.

The body has been known, however, to produce antibodies to some of its own native components. Immunologists hope to learn why this occurs and to devise ways of sensitizing the individual to his own cancerous tumors. This is being investigated.

Tissue and Organ Grafts

The extreme difficulty of grafting tissues or organs from one individual to another has challenged immunologists.

Rejection is believed by some to be caused by cell constituents which are antigenic to tissues not possessing those proteins. As a consequence, the recipient cells attack the transplant, presumably by generating antibodies which set up a harmful hypersensitivity in the foreign cells or destroy those cells outright. Others think that the transplant is attacked directly by the recipient's white blood cells.

There is support for the immunization theory. For example, a kidney transplanted from one man to his identical twin has developed normally, whereas most grafts from one person to another fail. Of course, identical twins have the same genetic makeup, the same blood antigens, and presumably the same cell antigens.

Under limited conditions and with careful controls, researchers have induced a state of immunological tolerance in prenatal or newborn animals. This has been accomplished by injecting intravenously into the young some spleen cells or whole blood from another individual of the same species. That produces immunological tolerance for a considerable period, though not necessarily for lifetime. Skin, endocrine tissue, bone, scale, toenail, or certain other tissues or organs from the original donor of the immunizing injection, grafted onto the "immunized" individual within its period of tolerance, have survived indefinitely, or at least much longer than grafts onto untreated individuals. This phenomenon, discovered in laboratory animals, is of special interest in human medicine. Our understanding is much too limited, however, to predict any practical applications to livestock health.

In further experiments, some inbred mice have accepted skin and organ grafts from each other. Some closely related chickens did likewise. Through a turkey study it is hoped to identify specific genes responsible for acceptance or rejection of grafts. If successful, attempts would be made to develop compatible lines through breeding. It is also hoped that extensive experiments will show what degree of relationship is necessary between donor and recipient for successful grafting.

Radiation Biology

Cell damage from excessive radiation, such as occurs from excessive exposure to X-rays and from atomic explosions is being intensively studied.

Immunologists are involved in these studies because excessive radiation destroys the antibody-producing cells and leaves the tissues defenseless against infection. Every effort will be made to learn how to restore the antibody-producing mechanism and reestablish normal immunities.

One approach to the problem is to graft normal tissues onto the injured individual. A means of propagating red bone marrow in glass and transplanting it to the injured individual would be particularly desirable. Red bone marrow is one of the most efficient antibody producers.

SCOPE OF IMMUNOLOGY

At the outset, it was suggested that immunological forces more than brute strength have brought the higher forms of animal life to their present stage. No class of animals is free of the forces.

As man has learned, and as he continues to learn, how these forces operate, he can use them deliberately for the improvement of livestock production and the general benefit of man.

Scientists learned long ago that they could apply the principles of immunology to the alleviation of suffering in man and animals. Producing better vaccines, and producing them more efficiently, have advanced this cause.

Now it is clear, more than ever before, that the antigen and the antibody, like the test tube and the microscope, are important tools in studying life processes generally. Immune reactions in the blood or tissue cells have an intimate relation to what goes on in the gene, the cytoplasm, or the invading pathogen.

Immunology is an engrossing subject, whether concerned with the combat of pathogens, the probing of the secrets of life generation, or the taming of the wild cell. Each new development extends the range and scope of this vital science.

Growth Through Agricultural Progress